OFFICIAL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Monty Krieger and Susan L. Acton

Serial No.: 08/765,108 Art Unit: 1646

Filed: March 27, 1997 Examiner: Michael T. Brannock

For: *CLASS BI AND CI SCAVENGER RECEPTORS*

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY TO EXAMINER'S ANSWER

Sir:

The following is in reply to the Examiner's Answer mailed April 7, 2004. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee Massachusetts Institute of Technology, Cambridge, Massachusetts, and licensee, Cardium Pharmaceuticals, Wenham, Massachusetts.

(8) ARGUMENTS

(a) The Claimed Invention

As discussed above under grouping of the claims, the claims are broadly divided into two groups: claims drawn to isolated nucleic acid molecules that code for scavenger receptor

proteins that are characterized by a defined binding affinity and methods for screening based on binding of the scavenger receptor proteins. The methods can be further divided based on the reagents and steps by which a particular object is achieved: (1) screening of compounds altering binding of SR-BI to LDL or modified LDL; (2) removing LDL from blood by reacting the blood with immobilized SR-BI; (3) inhibiting uptake of lipoproteins or lipids in adipocytes by inhibiting binding of the LDL to SR-BI; and (4) screening patients for abnormal SR-BI by measuring the amount or function of the SR-BI and comparing it to SR-BI in normal cells.

(b) Rejections Under 35 U.S.C. § 112

i. Rejection of Claims 11-13, 19-22 and 44-50 under 35 U.S.C. § 112, first paragraph (enablement)

The examiner's argument is that since the specification only provides a hamster and mouse cDNA encoding SR-BI, that no other polynucleotide molecule is either enabled or supported by the written disclosure. This conclusion is simply wrong.

SR-BI is defined in the specification based on its three dimensional structure (see Figure 1B), amino acid sequence (SEQ ID Nos. 4 and 8), and binding activity (binds native LDL, modified LDL when in the presence of 10% serum, and HDL). It has been demonstrated to be unique in all three areas, and **to exhibit complete identity in three dimensional structure and functional activity across all species and have very high sequence identity between species (see, for example, the printouts of the amino acid sequences for the SR-BI cloned from hamster, rat, mouse, human and cattle, showing the similarity between the proteins, as well as the hamster (SEQ ID NO 4) and murine (SEQ ID NO 8) amino acid sequences provided**

in the application). Further, from the latter, one can readily determine which amino acids are conserved between species and critical to function. Moreover, it is possible to detect SR-BI from one species with the DNA from another. As described in the application, Northern blot analysis of murine tissues was conducted using the hamster DNA), to show that SR-BI is most abundantly expressed in fat and is present at moderate levels in lung and liver. One skilled in the art, reading the phrase "SR-BI" or "scavenger receptor protein type BI" would know that this referred to a very particular type of protein. Based on the tissue expression data in the application, as well as the binding data, one skilled in the art would also know that it is involved in lipid transport, that it is highly unusual because it binds both native and modified LDL, that it binds cholesterol and HDL, and that it plays a role in steroidogenesis and transport of cholesterol to the liver, unlike any other scavenger receptor protein.

The legal requirement is not that every single possible nucleotide must be disclosed for the specification to support a claim to a genus. As the Court of Appeals stated in *Amgen Inc., v. Hoechst Marion Roussel, Inc. (now known as Aventis Pharmaceuticals Inc.) and Transkaryotic Therapies, Inc.*, 314 F.3d 1313 (Fed. Cir. 2003):

> We held in *Eli Lilly* that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself -- not merely a recitation of its function or a reference to a potential method for isolating it. 119 F.3d at 1566-67, 43 USPQ2d at 1406 (holding the disclosure of the cDNA sequence of the insulin gene of a rat did not adequately describe the cDNA sequence of the insulin gene of every vertebrate). More recently, in Enzo Biochem, we clarified that *Eli Lilly*

did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. *See Enzo Biochem*, 296 F.3d at 1324, 63 USPQ2d at 1613.

As the examiner correctly noted at page 4, a genus claim may be supported by a representative number of species. Here, two species were listed. The examiner concludes, with no legal or factual support, that it is not sufficient.

Importantly however, are that:

(1) the two disparate[1] species were highly homologous (and therefore one skilled in the art would have no trouble making a "consensus sequence" which looks like SR-BI in other species; this was confirmed by comparison with the human sequence;

(2) the cDNA was used to isolate and identify cDNA encoding SR-BI from other species, using only routine techniques: either hybridization or screening of a data base, and therefore other cDNAs could be similar isolated and identified;

(3) the amino acid and general structure (see page 23; figure 1) of the encoded protein was provided;

(4) the function of the protein and assays to screen for function were provided;

---

[1] The hamster, mouse and rat are all members of the family Muridae, however both mice and rats belong to the subfamily Murinae while hamsters belong to the subfamily Cricetinae.

(5) the cDNA was useful in obtaining the genomic structure, as proven by reference to the discussion in the patent cited by this Board in the decision previously rendered in this application and the Declaration under 37 C.F.R. 1.131.

Although the examiner rejected claims 44-50 as not supported by the specification and as not enabled, this is clearly wrong. These claims are drawn to a method for screening for compounds altering binding of SR-BI. Although it is possible some nucleotides hybridizing to either of SEQ ID Nos. 3 or 7 might not express functional SR-BI, certainly most (if not all) would and one skilled in the art should have no trouble expressing SEQ ID Nos 3 or 7 in cells and then screening for binding of LDL or modified LDL to the encoded SR-BI, as defined by claims 44-47; or removing LDL from blood by reacting the blood with immobilized SR-BI, encoded by SEQ ID Nos. 3 or 7, under the defined conditions, as defined by claim 48; or a method for inhibiting the activity of SR-BI as encoded by SEQ ID Nos. 3 or 7, as defined by claim 49; or a method for screening individuals for abnormal SR-BI activity where the only measurement is activity, not isolation or expression of a nucleic acid molecule encoding SR-BI, as defined by claim 50.

In so far as the Examiner is relying on *Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d. 1398 (CAFC 1997) as the basis for this rejection, Appellants note that *Regents of U.C.* is not applicable since the claims and underlying specification here are not analogous to the facts there. The Court in *Regents of U.C.* relied on the fact that the description of example 6 in the patent at issue prophetically described obtaining a cDNA sequence from the **protein** sequence of the human protein. This is completely different than the situation here,

where the specification relies on the use of the homologous cDNA as a probe, not a degenerate sequence obtained by reverse translation of a protein sequence. This difference is absolutely critical because the court in *Regents of U.C.* relied on their own precedence of *In re Deuel* 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (1995). The court stated, "A prior art disclosure of the **amino acid sequence** of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences encoding for the protein." In relying on the relationship of amino acid sequence to nucleic acid sequence, *Regents of U.C.* is limited to protein-to-DNA situations. It should be noted that the court in *Regents of U.C.* did not specifically address (and thus, did not overrule) the standard that has been accepted for the description requirement for the last 125 years, most recently explicated in *Vas-Cath Inc. v Mahurkar*. Notwithstanding the above, it is noted that only decisions handed down by an *en banc* panel of the Federal Circuit are sufficient to overrule previous case law. In this respect, the decisions of the Federal Circuit in *Eli Lilly* and its progenitor cases do not overrule the longstanding positions taken by the courts on the description requirements. (*Vas-Cath Inc. v Mahurkar).*

The examiner is ignoring the standard of those of skill in the art. One skilled in the art, presumably a Ph.D. in molecular biology, in the late 1990's, would have no trouble "envisioning" many different DNAs encoding SR-BI, once the amino acid sequences for two species, the structure of the proteins, the activity of the proteins, as well as two different DNAs encoding SR-BI from different species, were provided. Although it is recognized that *Fiers v.*

Sugano 984 F.2d 164 (Fed. Cir. 1993) is still good case law, the decision is based on science from a decade earlier – and this is a field that has evolved rapidly and drastically, allowing those skilled in the art to do many things routinely in the late 1990s that would have taken extraordinary effort in the late 1980s. In the 1980s one could not make large synthetic oligonucleotides; by the late 1990s, one could pick a contractor to make appropriate oligonucleotides.

This is equally responsive to the allegation that "an essentially limitless number" of polynucleotides is envisioned by the claims. This is not true. There are at least two limitations in the claims that exclude this possibility:

(1) the DNA must hybridize to SEQ ID NO. 3 or 7 under defined conditions (a temperature of approximately 25C below the melting temperature of a perfectly base-paired double stranded DNA);

(2) the DNA must encode a functional SR-BI which selectively binds to LDL and to modified lipoprotein having the characteristics of acetylated LDL in cell medium containing 10% serum.

SR-BI is known to those skilled in the art as having a particular amino acid sequence (regardless of which species it is, since it is highly conserved) and activity. There are only so many nucleotide sequence which could both encode such an amino acid sequence AND hybridize to SEQ ID No. 3 or 7 under the defined conditions. The examiner's comment that one skilled in the art would not know what changes could be made in the amino acid sequence is scientifically incorrect. First, it is well known which amino acids can be substituted for other

amino acids and still have similar protein structure (as determined by entering the amino acid sequence into anyone of a large number of commercially available computer programs AND by comparison of the two sequences described in the application from very different species). Second, one can readily test the activity to insure that activity is retained, as described by the assays in the application. The examiner's comment that predicting protein structure from sequence data makes no sense – for twenty years, one has been able to enter amino acid sequence into a computer and obtain the predicted structure. While predicting which portion of the protein is required for activity is more difficult, appellants are not claiming protein fragments, but DNA encoding the whole protein, which is easily screened for activity as described in the application.

While it is true that the specificity of nucleic acid interaction, or hybridization, can be affected by the conditions that the hybridization occurs under, those of skill in the art know how to perform hybridization experiments that lead to specific gene recognition of homologues, and the present application **specifically describes** how to do this for a SR-B1 cDNA. For example, on page 18, line 27 to page 19, line 6, there is an explicit description of a hybridization procedure in which the isolated hamster SR-B1 cDNA is used to produce a 600 base probe (derived from a BamHI restriction digest of the DNA shown in SEQ ID No. 3) which is used to probe different cell types from murine tissues and from 3T3 cells. The hybridization and washing conditions were done at 42° C and 50° C respectively using the well known conditions described by Charron et al. *Proc. Natl. Acad. Sci.* 86 2535-2539 (1989). Performing the hybridization analysis as described in the application clearly shows that a single predominant band of 2.4 kb was abundant in fat and present in moderate levels in lung and liver (page 31:line 11 to page 32:line 24).

While the 600 base probe derived from the hamster scavenger receptor type B1 cDNA hybridizes as a single gene sequence in mouse, a probe from CD36 has a different hybridization pattern, indicating that the hybridization assay described is sufficient to differentiate between CD36 and Appellants' nucleic acids encoding SR-B1 type proteins. This fact is significant since, as pointed out by the Examiner, other non-SR-BI genes are closely related in sequence to hamster and human SR-BI sequence (see Calvo et al.). This indicates that while CD36 and SR-B1 are related proteins (both members of the CD36 superfamily), they are not so related as to be considered homologues with each other and one skilled in the art would not interpret a reference to SR-BI as being the same as a reference to CD36; although CD36 is also excluded from the scope of the claim due to the binding specificity requirement: as shown in Figure 5, graphing competitive binding of acetylated LDL to either SR-BI or CD36 in the presence of native LDL, SR-BI binds native LDL and CD36 does not. This data also provides one skilled in the art with the information required to pick appropriate libraries for screening for DNA encoding SR-BI. See also pages 31-32 of the specification.

The mere fact that claims encompass embodiments that are not explicitly described, nor exemplified, does not render the claims non-enabled. In fact, inclusion of some embodiments that are even inoperative would still not render the claims non-enabled. As articulated by this Board in *Ex parte Mark*, 12 U.S.P.Q.2d 1904 (Bd. Pat. App. & Int'f 1989), "When it is considered that the claims remaining on appeal all require that the mutein produced retain the biological activity of the native protein, we consider the disclosure of this application to be enabling . . . The fact that a given protein may not be amenable for use in the present invention in

that the cystein residues are needed for the biological activity of the protein does not militate against a conclusion of enablement. One skilled in the art is clearly enabled to perform such work as needed to determine whether the cysteine residues of a give protein are needed for retention of biological activity." 12 U.S.P.Q.2d at 1906-1907.

These features therefore severely limit the number of polynucleotides that can be defined by the claims. Indeed, it was on similar facts and claim limitations that the Board allowed the claims drawn to the protein, in what is now U.S. Patent No. 6,429,289.

In summary, one skilled in the art, reading the claim which includes not only the phrase "hybridization" in conjuction with a defined sequence as well as the binding specificity of the SR-BI would know exactly what was defined by the claims. The claims are therefore supported and enabled, by the specification.

ii. Rejection of Claims 11-13, 19-22 and 44-50 under 35 U.S.C. § 112, second paragraph (definiteness)

The examiner has objected to the term "functional" as indefinite. This rejection is unfounded. The term is defined in the claims to mean the protein encoded by the DNA selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell medium containing 10% serum. The assays required to make this determination were described and exemplified in the application as filed. See, for example, pages 11-13, 16-17, 19-22, and Figures 2-8. The results not only demonstrate to one skilled in the art how to measure "function" as claimed, but that this is a very effective means of

distinguishing other proteins, even the closely related CD36 (which does not bind LDL and modified lipoprotein in the presence of cell medium containing 10% serum).

The response to the examiner's allegations regarding the breadth of the claimed definition of nucleotide molecule is found above. The claims define the claimed nucleotide molecule by reference to hybridization to either of two specific DNA sequences, SEQ ID No. 3 and 7, and provide the hybridization conditions. Those skilled in the art would have not trouble understanding what is meant by this language. Indeed, the examiner seems to acknowledge this point while arguing the fine points of what would, or would not, hybridize. The standard, however, is whether the claims would be definite to one skilled in the art, in view of the claim language and the specification. No evidence has been submitted otherwise.

Since the examiner has proposed language which he believes would overcome this point, thereby narrowing issues on appeal, an amendment accompanies this Reply Brief. However, it is the position of appellants that such an amendment is neither required nor to be construed as an admission that the claims in their current form are indefinite.

(c) Rejections Under 35 U.S.C. § 102/103

The examiner has rejected claims 11, 13, 19, 20 and 22 under 35 U.S.C. 102(a) as anticipated by Calvo, et al., J. Biol. Chem. 268(25) 18929-18935 (September 5, 1993).

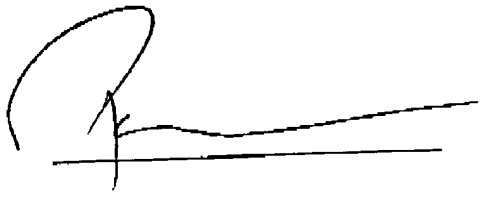
To the extent the claims are anticipated by Calvo, then the Declaration under 37 C.F.R. 1.131 must be sufficient to remove Calvo as a reference since the Declaration clearly demonstrates that appellants had cloned, and expressed, and measured the activity of, SR-BI prior to publication of Calvo.

Claims 11, 13, 20, 21 and 22 are not drawn to a DNA encoding SR-BI from a particular species. Therefore, it is sufficient to show that appellants conceived and reduced to practice the claimed subject matter prior to publication of Calvo. This they have done. The arguments that they did this with hamster DNA and Calvo had human DNA is irrelevant since the claims are not limited to human or hamster DNA.

Since Calvo did not know the identity of the CLA-1 protein, nor the activity of the protein, and indeed only expressed it as a fusion protein in order to determine its subcellular location, it would not have been obvious that one should express the protein in an expression vector, as defined by claim 21.

The patentability of claim 19 in view of Calvo is found in the appeal brief.

Respectfully submitted,



Patrea L. Pabst
Reg. No. 31,284

Date: June 7, 2004
PABST PATENT GROUP LLP
400 Colony Square Suite 1200
1201 W. Peachtree Street
Atlanta, GA 30361
(404) 879-2159
(404) 879-2160 fax